Future Developments in Chest Pain Diagnosis and Management.

Anthony FT Brown MB ChB, FRCP, FRCSEd, FACEM, FCEM

Professor of Emergency Medicine [1] and Senior Staff Specialist [2]

[1] School of Medicine, University of Queensland

[2] Department of Emergency Medicine, Royal Brisbane and Women's Hospital, Brisbane, QLD 4029, Australia

Tel: + 61 7 3636 7901

Fax: + 61 7 3636 1643

Email: af.brown@uq.edu.au

Louise Cullen MB BS (Hons), FACEM

Senior Lecturer [3], PhD candidate [4], and Staff Specialist [2]

[3] School of Medicine, University of Queensland

[4] School of Public Health, Queensland University of Technology, Brisbane, Australia

[2] Department of Emergency Medicine, Royal Brisbane and Women's Hospital, Brisbane, QLD 4029, Australia

Tel: +61 7 3636 7901

Fax: + 61 7 3636 1643

Email: louise-cullen@bigpond.com.au

Martin Than MB BS, FRCSEd(A&E), FACEM, FCEM

Senior Clinical Lecturer [5]and Consultant in Emergency Medicine [6]

[5] Christchurch School of Medicine, University of Otago, Christchurch, New Zealand

[6] Department of Emergency Medicine, Christchurch Hospital, New Zealand

Tel: + 64 3364 0270

Fax: +64 364 0286

Email: martinthan@xtra.co.nz

Address for Correspondence:

Professor Anthony FT Brown, Department of Emergency Medicine, Royal Brisbane and Women's Hospital, Butterfield Street, Herston, Brisbane, Queensland 4029, Australia.

E-mail: af.brown@uq.edu.au

Phone: +61 7 3636 7901

Fax: +61 7 3636 1643

Competing Interests:

Anthony Brown has received an honorarium from Elixir Healthcare Education.

Louise Cullen has received research support from Inverness Medical, Radiometer Pacific and Abbott, and an honorarium from Inverness Medical.

Martin Than has received research support from Abbott, Inverness Medical and Beckman-Coulter and an honorarium from Inverness Medical.

Key words: acute coronary syndrome; pulmonary embolism; aortic dissection; biomarkers;

Future Developments in Chest Pain Diagnosis and Management.

Introduction.

The clinician's approach to a patient with chest pain should first focus on excluding the most potentially serious causes such as acute coronary syndrome (ACS), pulmonary embolism (PE) and acute aortic dissection (AAD), all of which can present without immediately obvious clinical, laboratory, radiological or ECG findings. Once this initial phase of care is complete, there is then no consensus on who, if anyone, should assess the patient next. This increases the risk of recurrent pain and repeat presentations (1).

Alternate diagnoses at this stage include gastro-oesophageal reflux disease (GORD), musculoskeletal conditions including fibromyalgia, and psychological. These conditions are often diagnosed by the primary care physician based on response to a carefully chosen therapeutic trial, for instance of a proton-pump inhibitor (PPI) for GORD, or following specialist referral.

Much of the focus of research on patients with chest pain is directed at technological advances in the diagnosis and management of ACS, PE and AAD. This is despite the fact that there is no significant difference at four years as regards mortality, ongoing chest pain, and quality of life between patients presenting to the emergency department with non-cardiac chest pain (NCCP) compared to cardiac (2). Moreover, NCCP patients significantly outnumber patients presenting with an underlying cardiac cause, particularly to the primary care physician.

This chapter looks at future developments in the diagnosis and management of patients with suspected acute coronary syndrome, pulmonary embolism, aortic dissection, gastrointestinal disease and musculoskeletal chest pain.

Future Developments in Acute Coronary Syndrome

The diagnosis of acute coronary syndrome (ACS) is based on clinical judgement, serial 12-lead ECG analysis and cardiac biomarkers, and if these are negative some form of stress testing. Each of these modalities for the evaluation of a patient with potential ACS has difficulties. On the one hand any delay in the diagnosis or 'rule in' of an acute myocardial

infarction (AMI) precludes early pharmacological or interventional treatment known to improve outcome by limiting infarct size (3, 4). Conversely chest pain units aimed at ensuring significant diagnoses are not missed to 'rule out' patients with a low probability for ACS (5) report a negative assessment in up to 98% of all patients tested (6, 7). Despite this dichotomy in decision making perspective, still as many as 2-5% of patients with ACS, that is with either AMI or unstable angina pectoris (UAP), are missed and sent home from the Emergency Department (ED) (8).

Future developments in the assessment and management of patients with ACS presenting to the ED with chest pain will include improved ECG analysis, novel biomarkers, newer imaging techniques, risk stratification tools, improved drugs, sonothrombolysis and stem cell transplantation (see Table 1).

Earlier Diagnosis

The key to improving the outcome in the diagnosis of ACS lies in the development of a co-ordinated approach to early detection, from the time the patient first accesses medical care (9-11). Thus, pre-hospital diagnosis of ST-elevation myocardial infarction (STEMI) with 12-lead ECG analysis can facilitate the primary goal of immediate opening of the infarct-related vessel, for instance by direct transfer of the patient to a hospital operating a catheter laboratory 24-hours a day (10-12).

Body surface mapping

Standard 12-lead ECG analysis identifies ST-segment elevation myocardial infarction (STEMI) and dictates the need for immediate reperfusion therapy for an optimal outcome (13-15). However, neither the ECG nor serum biomarkers have high early sensitivity to detect acute myocardial infarction (AMI) in general, as they may remain negative immediately post event. One option to improve the sensitivity in detecting AMI is ECG body surface mapping (BSM), that uses up to 80 ECG leads placed on the anterior and posterior chest to enable more complete visualisation of cardiac electrical activity (See Figure 1).

The BSM output can be displayed in a 12-lead ECG format, an 80-lead format or on colour contour or topographical maps (16). With recent advances in computer technology, BSM has become more 'user-friendly' to aid direct visualisation of injury patterns particularly in the right ventricle and posterior wall of the left ventricle associated with an inferior AMI (17, 18).

Body surface mapping may also improve the diagnostic evaluation and treatment of patients with ST-depression on a standard 12-lead ECG. In particular, BSM can differentiate a group of patients who in fact have ST elevation on BSM, who theoretically might therefore benefit from early reperfusion therapy (19, 20). One BSM trial has also shown the ability to detect AMI pre-hospital (21). However, early detection of AMI with BSM comes at a cost of a lower specificity and higher false negative results compared to the standard ECG (22).

High frequency QRS analysis

Another approach to improve the detection of acute myocardial ischemia is ECG analysis of the high frequency (HF) components of the QRS complex above 100 Hz (23, 24). These frequencies are usually not seen as notable morphological alterations in the QRS complex on the standard 12-lead ECG machine, as these use noise-reducing filters to eliminate this high frequency range. However, the HF components can provide information about the severity of ischaemia and MI. Although HF-QRS analysis may offer additional non-invasive information in acute coronary syndromes, it is currently hampered by marked inter-patient variance, and a lack of large scale clinical outcome trials in humans (24).

Novel ACS Biomarkers

Overview

Elevation of cardiac biomarkers is pivotal to the diagnosis of AMI (25). However biomarkers that could detect ACS without myocardial necrosis may allow clinicians to recognise biological events happening before necrosis occurs, thereby identifying earlier patients at higher risk of an adverse event (26, 27). This could then lead to treatment targeted to limit or prevent an AMI. At present, these types of biomarker are not yet commercially available.

Although cardiac troponins provide important prognostic information, they do not accurately determine absolute risk for ACS (28). A number of newer cardiac biomarkers have therefore been proposed for the diagnosis and risk stratification of patients with possible ACS. These include copeptin, myeloperoxidase (MPO), pregnancy associated plasma protein A (PaPP-A), placental growth factor (PlGF), CD40 ligand, ischemia modified albumin (IMA), fatty acid binding protein, free fatty acids (FFA), growth differentiation factor–15 (GDF-15), serum choline, glycogen phosphorylase isoenzyme BB (GPBB) and high sensitivity CRP (hsCRP) (see Table 2). Although many of these may provide additional short and long term prognostic information, at present none offer a clear diagnostic advantage over troponin (Tn) alone. In addition, few are currently available in commercially approved kits.

Copeptin

Copeptin, the c-terminal part of the vasopressin prohormone, is secreted from the neurohypophysis and is activated in the endogenous stress response (29). The measurement of copeptin in addition to a biomarker with a different pathophysiological origin such as troponin can improve the diagnostic accuracy at presentation, and possibly eliminate the need for serial sampling. One study by Reichlin et. al. found that combining copeptin and troponin T had a sensitivity of 98.8% and a specificity of 77.1% for diagnosing AMI. (29).

Myeloperoxidase

Myeloperoxidase (MPO) is released by neutrophils and macrophages and so becomes elevated in coronary artery atherosclerotic lesions prone to rupture (26, 30). It has shown promise in risk stratification of chest pain patients with persistently normal troponin levels, and may prove useful for the disposition of patients from the Emergency Department. Interestingly, MPO levels have been found to be elevated at baseline in patients subsequently shown to have AMI, even when symptom onset was less than 3 hours before blood analysis (30). However MPO elevation is not specific to cardiac disease, as activation of neutrophils and macrophages occurs with many other disease processes (26).

Pregnancy associated Plasma Protein A

Pregnancy associated Plasma Protein A (PaPP-A) is a marker of neovascularisation that may also play a role in detecting atherosclerosis and plaque rupture (26, 31). Although

PaPP-A appears to have little correlation with other cardiac biomarker levels, it has shown promise at predicting the need for a revascularization procedure (31, 32).

Placental Growth Factor

Placental Growth Factor (PlGF) is a hormone that stimulates angiogenesis and macrophage recruitment (32), and may thus indicate inflammation predicting early acute myocardial infarction (26). However, studies to date used the higher cut-off values for the cardiac troponin reference standard that are now superseded, so new research comparing PIGF with the currently recommended levels for abnormal troponin is now necessary to re-confirm its efficacy (31).

CD40 Ligand

CD40 Ligand levels reflect both inflammation and platelet/plaque interactions (32), with encouraging results particularly when combined with PlGF (26, 31). More studies are needed before strong conclusions can be drawn.

Ischemia modified albumin

Ischemia modified albumin (IMA) molecules are produced when the metal terminus of the albumin molecule is damaged during ischaemia (31, 32). IMA should thus be useful for its strong negative predictive value for ischemia, even prior to necrosis. Current studies indicate good potential for IMA to rule-out ACS when combined with troponin and an ECG (32). However it is currently difficult to assess the role of IMA due to the lack of standard reference criteria for non-necrotic ischaemia (31). It may also not be specific for cardiac ischaemia (26).

Fatty Acid Binding Protein

Fatty Acid Binding Protein (h-FABP) is released rapidly post-infarction (31), and may outperform myoglobin in the early detection of acute myocardial infarction. However current studies indicate that h-FABP lacks specificity (31), and adds little diagnostic information to the newer ultra-sensitive troponin assay results (33).

The real value of any new biomarker, including genetic and genomic markers, will be to better define ACS disease activity, and or to refine the risk stratification process, particularly by identifying ischaemia without myocardial necrosis in ACS.

Multi-marker Approach

Combinations of biomarkers which complement each other in terms of their release curve improve the accuracy of the early detection of AMI, and so should reduce the delay to key interventions (34-38). In addition, multi-markers are able to rapidly rule out AMI with a high negative predictive value (35, 37, 39, 40). The ability to safely and accurately exclude or 'rule-out' AMI improves the efficiency of a chest pain assessment unit, and/or will allow earlier stress testing in the biomarker negative group leading to a shorter hospital stay.

Delta Troponin and Ultra-sensitive Troponins

The use of delta troponin, the change in the troponin value over time, has improved the diagnostic accuracy for AMI (41-43). Newer ultra-sensitive troponin assays may be able to utilise very low levels of detection, and employ a 'delta approach' that measures change between initial and incremental levels at zero and from two to six hours after the onset of symptoms, or from hospital arrival (44, 45).

Unfortunately, the list of conditions other than myocardial ischaemia associated with an elevated troponin continues to increase. Characteristic changes in troponin levels associated with many non-ACS related diagnoses such as pulmonary embolism and sepsis are not well defined. Thus, exquisitely sensitive assays may well produce their own problems in interpretation, in the light of the already long list of medical conditions associated with a raised troponin level even at currently agreed cut-off levels (46). This will be a particular problem if the newer ultra-sensitive troponins are used indiscriminately, without careful consideration of need from the medical history and examination findings.

Newer Imaging Modalities

The choice of objective tests to identify ACS has expanded in recent times to include cardiac computed tomographic angiography (CCTA), plaque composition analysis, cardiac magnetic resonance imaging (CMR) and positron emission tomography (PET) (see Table 3).

Cardiac computed tomographic angiography

High resolution cardiac computed tomographic angiography offers non-invasive coronary angiography that may improve risk stratification, particularly in the intermediate risk

chest pain patient (47). CCTA allows evaluation of global and regional left ventricular function comparable to cardiac MRI (48). It also provides information about luminal narrowing and plaque composition. Several clinical and economic studies support the use of CCTA scanning to risk stratify ED patients with ACS (49-55). Although radiation dose is an issue, when negative CCTA should allow the definitive rule-out of coronary artery disease in the low and intermediate risk group (56).

Plaque composition analysis

Plaque composition analysis may also prove of particular use in predicting significant ACS (57), as these patients have more mixed and non-calcified plaques than patients with stable angina (58, 59). Outcome data on plaque analysis by CCTA are limited, but it may provide additional prognostic information for patients with possible ACS.

Alternatives to CCTA aimed at the early diagnosis of a 'vulnerable' plaque include intravascular ultrasound (IVUS), palpography and virtual histology, optical coherence tomography (OCT) and near infrared spectroscopy (60) (see Table 3). However there is at present little evidence that a local or regional therapeutic approach to asymptomatic 'vulnerable' plaque reduces cardiac events compared to current optimal systemic therapy (60).

Cardiac MRI

Cardiac MRI (CMR) is already established in the assessment of congenital heart disease, the great vessels, pericardial disease and chronic coronary artery disease. It also allows the assessment of a wide spectrum of causes of chest pain [52]. Although coronary anatomy imaging using coronary artery CMR has been developed, few studies have assessed the clinical utility of CMR for ACS in the ED setting (61).

CMR may be a useful alternative investigative pathway in view of its lack of radiation exposure. In addition, stress-CMR using adenosine or dobutamine may help to predict significant coronary artery disease (62, 63), and may have a role in a select group of patients as an alternative non-invasive stress test (64).

Positron emission tomography

As not all coronary stenoses detected by CCTA are flow limiting, additional non-invasive testing should be considered prior to cardiac catheterisation. Positron emission tomography (PET) hybrid CT devices allow integration of the structure and function of the heart (65). Stress PET data may identify a haemodynamically significant stenosis, and when combined with the anatomical information from the CCTA help guide revascularisation decisions (65, 66). Again further research is needed to define its exact role in the management of ACS in the ED setting, although access will remain limited for some time yet.

Risk Stratification Tools

Risk stratification tools are essential in determining pre-test probability (PTP), as no single clinical feature and or investigation result alone is diagnostic for acute coronary syndrome (67). Accurate estimation of the PTP for ACS is fundamental to the appropriate use of resources. A number of methods to determine pre-test probability for ACS have been reported including the physician's own estimate (68), decision trees (69), logistic regression (70, 71), attribute matching (72, 73), and computer-based artificial neural networks (74).

Kline et al determined that in a population with a pre-test probability of ACS of less than or equal to 2%, the risk of testing will exceed its benefits (73). Unnecessary investigations in this group are then averted as the person is already at a very-low risk of ACS (68).

PREtest ConsultACS™

A computer-derived, quantitative pre-test probability assessment derived from attribute matching has been developed for use in ACS, as well as in PE (see later). PREtest ConsultACS™ (PREtest Consult Inc™, Charlotte, North Carolina) matches an 8-component clinical profile from any individual patient considered at risk of ACS, with a 14 800 prior patient reference database to allow an estimate of PTP probability. Those with a PTP of ≤ 2% or 'test negative' have a 45 day ACS outcome of just 0.3% (75). Prospective validation in other non-USA populations is in progress.

However, many models still focus on ruling in the diagnosis of AMI to facilitate the early and appropriate use of cardiology services, rather than excluding ACS by clearly identifying a rule out population suitable for early ED discharge (76, 77). Thus the use of these tools is currently restricted by their heterogeneity and different end-point intention (78). This emphasises the importance of adopting a standardised data definitions set for use in ACS research. These standardised data definitions will ensure use of a common language and framework to maximise value when extrapolating research findings between different studies(79).

Treatment Advances

Antiplatelet medication

Early diagnosis allows the earlier initiation of treatment for STEMIs and NSTEMIs, and improved outcomes. Antiplatelet medication is central to the treatment of ACS, such that aspirin is now widely used in virtually all patients with undifferentiated chest pain. This indiscriminate use of aspirin, despite significant benefit for those with ACS-related diagnoses, currently lacks validation, but is assumed to be safe.

Clopidogrel is another common antiplatelet medication used with aspirin, but it shows variability in platelet inhibition (80, 81). Alternative dual antiplatelet treatment options include newer therapies such as prasugrel, which received Food and Drug Administration (FDA) approval in early 2009, and ticagrelor both of which show improved platelet inhibition (82-84). Ticagrelor is an oral, reversible, direct-acting inhibitor of adenosine diphosphate receptor P2Y12 that has rapid, pronounced platelet inhibition. It has the advantage of a survival benefit without an overall increased rate of major bleeding when compared with clopidogrel (85).

The use of other platelet inhibitors such as the glycoprotein IIb/IIIa (GP IIb-IIIa) inhibitors in the setting of STEMI has shown variable changes in coronary artery patency (86-88). While one small trial of pre-hospital treatment with a glycoprotein IIb/IIIa inhibitor did not show clinical benefit (89), a larger study is underway investigating the benefit of early GP IIb/IIIa inhibition prior to percutaneous coronary intervention (PCI) in the setting of non-ST elevation acute coronary syndrome (NSTEACS) (90).

Sonothrombolysis

Another emerging approach to improving vessel patency is sonothrombolysis using low-frequency ultrasound for thrombus dissolution. This may become a valuable non-invasive technique to improve vessel patency with thrombolytic therapy, in the large majority of patients unable to access timely percutaneous interventions (91). Low frequency ultrasound treatment increases tissue perfusion from coronary occlusion by thrombus dissolution (92).

Stem cell transplantation

Finally stem cell transplantation to improve the function of the injured myocardium is under investigation (93). Intracoronary injection of mononuclear bone marrow cells in patients with a recent MI appears safe (94). 'Cellular cardiomyoplasty' trials administering intravenous allogenic human marrow stem cells (MSC) without immunosuppression to post-AMI patients are currently underway (95).

Future Developments in Pulmonary Embolism

The decision whether to investigate a patient for a particular disease is a balance between the risks of harm from missing the diagnosis, against the harm that might derive from the investigations themselves. As regards pulmonary embolism (PE), the threshold at which clinicians decide to commence investigating is dropping steadily (96), and current strategies in the assessment of a patient with a suspected PE certainly have the potential to cause harm. This is due to widespread indiscriminate use of D-dimer testing, from fear of missing the diagnosis, that leads to increased diagnostic imaging by CT pulmonary angiogram (CTPA) following from the high false positive rate of the D-dimer assays. This in turn increases cost, causes delay with ED overcrowding, and exposes patients to the risks of unnecessary ionising radiation and contrast nephropathy.

Similar to ACS, future developments in the assessment and management of patients presenting to the Emergency Department with chest pain suggestive of PE again include novel biomarkers, newer imaging techniques, risk stratification tools and improved drugs.

Additional strategies include percutaneous mechanical thrombectomy and re-evaluation of the role of thrombolysis in submassive PE (see Table 4).

Novel PE Biomarkers

Many novel biomarkers involved in inflammation, haemostasis and vascular injury are under investigation to replace or supplement D-dimer testing in PE. Nordenholz et al investigated 50 potential biomarkers for their predictive value in 304 ED patients evaluated for PE, and found that only D-dimer, C reactive protein (CRP) and myeloperoxidase (MPO) demonstrated sufficient diagnostic accuracy to support their use clinically, with areas under the receiver operating characteristic (ROC) curve of >0.75 (97).

D-dimer testing using multiple rather than single cut-off levels

D-dimer testing in clinical practice is currently based on a single cut-off level for a positive and a negative result created using ROC curve analysis. Whilst this dichotomous approach makes the test result easy to interpret, it is over simplistic and fails to indicate how far above or below the cut-off the test result actually lies. Linkins et al have suggested that the use of three probability-specific D-dimer cut-off points can exclude PE in a greater proportion of patients than using a single cut-off point, without sacrificing the negative predictive value (98).

Ischemia-modified albumin

Whilst levels of ischemia-modified albumin are also being investigated for their diagnostic utility in ACS, a recent animal study has suggested that ischemia-modified albumin levels increase within one hour and up to the sixth hour post pulmonary embolism (99). It is unclear though how IMA might, if at all, usefully discriminate between different underlying causes in a patient with undifferentiated chest pain.

Growth arrest-specific gene 6

Growth arrest-specific gene 6 (Gas6) is a protein that is elevated during pulmonary or systemic infection, but not with PE. As D-dimer levels rise in all these conditions, the addition

of Gas6 testing may help reduce the false positive rate for PE thereby increasing the specificity of the D-dimer test (100).

Myeloperoxidase (MPO)

MPO correlates with the presence of PE with an area under the ROC curve (AUC) of 0.78 compared to 0.93 for D-dimer, with a negative test helping rule out a PE (97). MPO may also have additional diagnostic utility again used in conjunction with D-dimer, as a combination approach reduces the high false positive rate from using D-dimer alone (101).

Tissue Plasminogen Activator and Plasminogen Activator Inhibitor-1

Once fibrin is formed in the thrombosis / fibrinolysis process, tissue plasminogen activator (tPA) activates plasminogen to plasmin to begin fibrin breakdown, with one of the subsequent breakdown products being D-dimer. This process is partly regulated by plasminogen activator inhibitor type-1 (PAI-1). Both tPA and PAI-1 are detectable in the circulation using an enzyme-linked immunosorbent assay (ELISA) once fibrinolytic system activation has occurred. Preliminary research has suggested very high sensitivity for tPA and PAI-1 in the detection of PE, but their clinical correlation is unclear.

Imaging

Various new imaging techniques are being investigated including single photon emission computed tomography (SPECT) perfusion lung scan, magnetic resonance imaging angiography (MRA) and magnetic resonance venography of the veins of the thighs (MRV).

Single photon emission computed tomography (SPECT) perfusion lung scan

This nuclear medicine technique uses images in extra planes from a double or triple-head camera, and has a better specificity than ventilation perfusion (VQ) planar scanning, with less scans reported as ‘indeterminate’ or non-diagnostic (102, 103). Currently there are relatively little published data on its clinical use.

Magnetic resonance imaging angiography (MRA)

Experience with MRA is much more limited than for VQ and CTPA scanning. Therefore MRA is usually restricted to patients with contraindications to conventional imaging. Gadolinium-enhanced angiography (Gd-MRA) has demonstrated a specificity for PE in the high ninety percent range, with a sensitivity ranging from 85-100%, although there is concern about the incidence of nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy (NSF/NFD) in patients given gadolinium contrast. The FDA is monitoring the situation especially in patients with moderate (GFR <60 mL/min) to severe renal disease. Alternate contrast techniques using contrast specifically targeting thrombus such as iron oxide microparticles, single chain antibodies and T1 bright methaemoglobin are under investigation.

PIOPED III.

A prospective multicentre investigation to determine the diagnostic accuracy of Gd-MRA of the pulmonary arteries in combination with magnetic resonance venography of the veins of the thighs (MRV) in patients with clinically suspected acute PE is currently underway, known as Prospective Investigation of Pulmonary Embolism Diagnosis III (PIOPEDIII).

The aim is to recruit around 1,200 patients with suspected acute PE over a period of two years using composite reference standards to diagnose venous thromboembolism (VTE) and exclude PE. All patients with PE and a matched group without PE will undergo Gd-MRA/MRV. This combination technique could eliminate the need for iodinated contrast material and ionizing radiation in the estimated 24% of patients with suspected PE, who have relative contraindications such as renal impairment, allergy, and pregnancy (104).

ThromboView™

ThromboView™ (Agen Biomedical, Brisbane Australia) consists of ^{99m}Tc labelled de-immunised anti-crosslinked fibrin (anti-D-dimer) Fab' fragments with a high affinity and a high specificity for D-Dimer given intravenously. ThromboView™ is under investigation as a diagnostic tool for thromboembolic events such as PE detected by SPECT. ThromboView™ may be superior to conventional imaging by selectively disclosing acute thrombi, as it is able to distinguish between a fresh thrombus and other filling defects within the pulmonary arteries

(105). (106) A recent phase II study showed only comparable sensitivity and specificity to CTPA for PE. Phase III trials are in progress.

Decision Analysis Risk Stratification

Various new techniques are being used to provide an actual point-estimate of pre-test probability (PTP) of PE, over and above the physician's usual unstructured Gestalt estimate, assisted by validated scoring systems such as the Canadian (Wells) or Geneva scores. These include a back-transformed logistic regression equation, and non-linear models such as artificial intelligence or Bayesian Network analysis (107-109).

Probability Software Database tools

PREtest ConsultPE^{TM} (PREtest Consult Inc^{TM,} Charlotte, North Carolina) is a novel computerised method of pre-test probability assessment derived from a process called attribute matching. This requires the clinician to enter 10 predictor variables into a computer program *(age, ± pleuritic chest pain, ± dyspnea, pulse oximetry reading, heart rate, ± prior VTE, ± recent surgery or trauma, ± oestrogen use, ± haemoptysis, ± unilateral leg swelling).*

Attribute matching works by a selection process whereby a computer algorithm compares the results of all ten predictor variables obtained from the patient being evaluated to a library of 12,595 research patients previously evaluated for PE compiled from multiple hospitals. The algorithm returns only the "matched" patients who share the same profile of predictor variables as the patient under consideration. It then reports the proportion of patients with disease in this matched sample as a pre-test probability, that is the number of diseased patients divided by the total number of patients who fit the profile (see Figure 2).

The utility of PREtest ConsultPE^{TM} includes two discrete steps. The clinician assesses the pre-test probability of PE using a validated tool, and if the probability is low enough, no further testing is warranted. Other decision rules such as the 'Charlotte Rule' were derived to allow the exclusion of a PE, but those exclusion criteria function in an 'all or none' way without allowing integration into a continuum of testing available with PREtest ConsultPE^{TM} (110, 111)

The ‘test threshold’ for PE has previously been estimated at 2% (97, 106, 107), which is the pre-test probability that should be exceeded to justify the need for diagnostic testing. Prospectively, the summary 45-day outcome rate has been found to be 0.7% for the whole subgroup of patients with a PTP between zero and 2%. Although local standards may vary, the 1% threshold probably represents a reasonable international threshold to exclude PE (73, 110, 112, 113). Therefore, if the patient’s pre-test probability is zero to 2%, the risks inherent in further evaluation secondary to unwarranted treatment in the event of a false-positive test result, outweigh the risks of the PE. Thus a patient with a quantitative PTP ≤2% for PE does not need a D-dimer, nor a CTPA, nor any other pulmonary vascular imaging study, saving time, cost and risk.

Moreover, those patients with a PTP above 2% may still be able to avoid exposure to unnecessary ionizing radiation by next adding biomarker testing to then produce a post-test probability again below 1% (see Figure 3, green rectangle). Knowing that quantitative immunoturbidimetric or enzyme-linked colorimetric D-dimer assays demonstrate a LR(-) = 0.10-0.15 for the diagnosis of PE (114-116), a pre-test probability of PE <7.5% followed by a negative D-dimer test result of <500 ng/mL then produces a post-test probability <1%. Once again, this rules out a PE without the need for any imaging.

Improvements in Therapeutic Agents

Several new therapeutic agents including parenteral and oral anticoagulants have been studied.

Parenteral anticoagulants

Idraparinux is derived from fondaparinux and binds to antithrombin with such high affinity that its half-life is comparable to that of antithrombin itself. The advantage of idraparinux is that it may be given by subcutaneous injection once-weekly, and does not require coagulation monitoring. However, it must be used with caution in patients with renal insufficiency as it is excreted via the kidneys, and is contraindicated in patients with a creatinine clearance of less than 30 mL/min. Protamine sulphate, used to counteract heparin, does not reverse the anticoagulant effects of idraparinux.

SSR 126517 shares the pharmacological features of idraparinux, but with the advantage that its anticoagulant effect is reversed by giving intravenous avidin, a tetrameric glycoprotein.

Oral anti-coagulants

Warfarin

Warfarin is currently the only orally available drug for long term anticoagulation. Several problems make warfarin a difficult drug to use for both physicians and patients alike. These include a narrow therapeutic margin, delayed onset of action, difficulty with reversal, many interactions with drugs and diet, a wide variation in anticoagulant effect and the need for frequent laboratory monitoring. These may lead to recurrent thrombosis from undertreatment or to excessive bleeding with overtreatment. Bleeding complications with warfarin are among the most frequent adverse drug effects, with the risk of major bleeding between 1% and 5% per year. Therefore there is an ongoing search for a replacement for warfarin for oral anticoagulation. Newer oral agents with fewer side effects than warfarin have undergone trials in venous thromboembolism (VTE) prevention, but treatment trials currently are limited and usually restricted to therapy for DVT. These agents include dabigatran etexilate, rivaroxaban and apixaban.

Dabigatran etexilate, rivaroxaban and apixaban

Dabigatran etexilate is an oral small molecule pro-drug that acts as a thrombin inhibitor, whose absorption is pH sensitive and is reduced by around 30% by proton pump inhibitors. Effective doses of dabigatran etexilate are relatively high, and it is contraindicated in patients with renal failure, as it is excreted via the kidneys. Rivaroxaban selectively inhibits factor Xa and is administered orally with 80% bioavailability. It must also be used cautiously in patients with renal insufficiency or in patients with severe liver disease, and is monitored by Factor Xa inhibition. Finally apixaban is an orally administered selective inhibitor of factor Xa, that can be monitored using a factor Xa inhibition assay, or a diluted prothrombin time.

It is hoped that these agents will provide a better therapeutic window, easier monitoring and may be simpler to reverse in an emergency, making them more convenient and safer to use than warfarin.

Percutaneous Mechanical Thrombectomy

Percutaneous mechanical thrombectomy (PMT) by mechanical fragmentation and thrombus aspiration is a novel approach that may benefit patients with massive PE and right ventricular dysfunction. Patients who may particularly benefit would be those with major contraindications to thrombolysis, those at an increased bleeding risk, after failed thrombolysis or when surgical thrombectomy is unavailable. Clot is fragmented via catheterisation, and the fragments removed via an internal aspirator (117).

Thrombolysis for PE

Although meta-analysis has shown no benefit for thrombolysis in patients with PE without shock (118), these patients have significant morbidity at 6 month follow-up, with a 41% rate of cardiopulmonary problems, either right ventricular dysfunction on echo, heart failure (NYHA score >II) or a 6 minute walk distance (6MWD) of < 330 m (119).

The Pulmonary Embolism Thrombolysis (PEITHO) study being conducted in Europe is seeking to demonstrate whether thrombolysis with tenecteplase plus standard anticoagulation improves the outcome of patients presenting with high-risk sub-massive acute pulmonary embolism, when compared to standard anticoagulation alone. Currently around one third of the target of 1000 patients have been recruited.

Future Developments in Acute Aortic Dissection

Acute aortic dissection (AAD) is one of the most common catastrophes of the aorta classically affecting males aged 50-70 with hypertension, with sudden severe chest or back pain and a myriad of other possible symptoms and signs. It is time-critical and rapidly fatal if left untreated, particularly for ascending type A dissections (120).

Future developments in the assessment and management of patients with AAD presenting to Emergency Department with chest pain will once again include novel biomarkers, plus newer imaging techniques such as contrast-enhanced ultrasound, endovascular treatment and combined interventional and surgical treatment (see Table 5).

Novel AAD Biomarkers

Serum smooth muscle myosin heavy chain, calponin, D-dimer and serum soluble elastin fragments are promising tests to help rule in or rule out the diagnosis of acute aortic dissection (121, 122).

Serum smooth muscle myosin heavy chain

Serum smooth muscle myosin heavy chain is specific for damage to the smooth muscle of the arterial wall, with diagnostic studies yielding a sensitivity of 90.9% and a specificity of 98% within 3 hours of symptom onset of suspected acute aortic dissection, particularly with proximal lesions (123).

Calponin

Likewise immunoassays against basic and acidic calponin, the troponin-like protein of smooth muscle, have shown potential to detect AAD in the first 6 - 24 hours. The moderate sensitivity and specificity suggest that technical improvements in the assay are still necessary before firm recommendations on its use can be made (124).

D-Dimer

D-Dimer has been used for many years when negative to rule out thromboembolic diseases such as DVT and PE. A recent Austrian study supports the routine measurement of D-dimer to exclude acute aortic dissection (AAD), with 100% negative predictive value (NPV) for a cut-off level of 0.1 µg/mL (125). However the optimal cut-off value for its clinical use is still disputed (126).

International Registry of Acute Aortic Dissection (IRAD) data on D-dimer

Investigators from the International Registry of Acute Aortic Dissection (IRAD) have just published a sub-study on biomarkers (IRAD-Bio) focusing on D-dimer (121) in AAD. Although small, the study was one of the largest collections of proven AAD patients within a prospectively enrolled cohort of 87 positives out of 220 patients with suspected acute aortic

dissection. At the widely used D dimer cut-off level of 500 ng/mL, a negative D-dimer had a sensitivity of 95.7% within six hours of the onset of symptoms. In addition, the authors also noted that D-dimer was markedly elevated in AAD and suggested that using a D-dimer of ≥1600 ng/mL was useful as a 'rule in' cut-off to identify patients with a high probability of AAD. However the diagnostic accuracy among patients with AAD is dependent on the type, extent, and the time from presentation.

Serum soluble elastin fragments

Although the structural protein serum soluble elastin fragments begins to leak from the aorta during the aging process, acute aortic injury causes serum levels to elevate sharply. Testing has shown early promise with a high predictive value, but as the test takes up to three hours to perform, it is likely to be unacceptable given the urgency of the condition.

Contrast-enhanced Ultrasound (CEUS)

Contrast-enhanced ultrasound involves introducing gas filled microbubbles into the circulation to provide strong contrast on ultrasonography. These microbubbles can be modified to target certain tissue types, such as inflamed blood vessels allowing CEUS to evaluate abdominal aortic dissection, particularly in patients with contraindications to CT contrast agents such as renal failure or severe allergy. CEUS may allow a more rapid and non-invasive diagnosis, especially in critical patients from intensive care units, because of its bedside availability. As the examination is dynamic, additional information about blood flow in the true and false lumen and about renal perfusion after dissection can be obtained. Thus CEUS may provide a good alternative to multi-slice computed tomography angiography (CTA) (127).

Endovascular Treatment

Stanford type B aortic dissections confined to the descending, distal aorta have traditionally been managed medically, but this is changing with the advent of endovascular stenting with careful patient selection. Recent generations of stent-grafts are able to avoid many of the earlier stent complications such as stroke, penetration of the aorta, graft collapse,

leak, migration or aneurysm extension, although evidence of longer term durability is unclear (126).

One concern is still the radiation exposure of regular CT imaging of stents needed to ensure their integrity and placement, particularly in younger patients (128).

Combined Interventional and Surgical Treatment

The combination of surgical aortic reconstruction with endovascular stent-grafting has been shown to simplify type A aortic dissection management, reduce the circulatory arrest time, reduce the risk of surgical complications and reduce the need for subsequent surgery on the descending aorta. Again the long-term effectiveness has not been studied (129).

Triple 'Rule-Out' Scan

CT angiography is the imaging modality of choice in both the investigation of PE and acute aortic dissection (AAD). Now that cardiac CT angiography (CCTA) is becoming established, some have suggested using a modified scanner protocol aimed at simultaneously investigating for all three of PE, AAD, and coronary artery disease (CAD), known as the 'triple rule-out scan'.

Previously such scans were precluded as patients would have had to hold their breath for over 30 seconds to obtain adequate images from the lung apices to the diaphragm in older generation scanners. The advent of 64 and 128 slice CT scanners allows a faster scanning process and reduced movement artefact. Technical challenges still remain, in particular achieving consistent high levels of contrast intensity in all three vascular zones. Also it is difficult to simultaneously image segmental pulmonary arteries and the distal coronary arteries supplied by the right and left ventricles respectively.

A saline bolus to flush contrast out of the right side of the heart is used to obtain high and consistent visualisation of the coronary arteries with minimal right heart enhancement in CCTA, whereas CTPA protocols are designed to achieve maximal enhancement of the pulmonary arteries and the right side of the heart. Therefore triple rule-out scans require precise harmonisation of contrast injection and imaging sequences(130) .

Radiation dosage issues

The exact radiation dose to the patient from a triple rule-out scan appears to be highly variable, depending upon the scanner protocol used. For instance the effective radiation dose can be reduced by over 50% to 8.75 ± 2.64 mSv with ECG-based tube current modulation without loss of image quality (131). As traditional imaging studies for ACS and PE involve a chest radiation dosage as low as 5 mSv or less, this still represents a significant step up, so poor patient selection and indiscriminate use of the triple rule-out scan would have significant radiation exposure issues.

As scanner technology and contrast protocols improve the challenge for clinical leaders will be how to focus its use to avoid spiralling costs and excessive patient radiation exposure.

Future Developments in Gastrointestinal Disease

Gastro-oesophageal reflux disease (GORD) is the most common cause of oesophageal chest pain, although the majority (60%) of patients have no evidence of erosive oesophagitis at conventional endoscopy. Such non-erosive reflux disease (NERD) by definition should still respond to acid suppression therapy such as a proton-pump inhibitor, albeit with a lower response rate than in erosive GORD (132)

Novel endoscopic techniques

Novel alternate upper GI endoscopy techniques are available to demonstrate subtle submucosal abnormalities such as chromoendoscopy with Lugol's iodine, confocal endomicroscopy, or narrow band imaging in conjunction with zoom magnification (132). Their exact indication is unclear, as is the role of 24-hour pH and impedance monitoring in NERD.

In addition finding an objective marker to differentiate NERD from functional heartburn might better guide empiric therapy, as the latter is a symptom complex unrelated to the reflux of gastric contents with no correlation of symptoms with acid reflux exposure (132).

Non-GORD-related oesophageal chest pain

A large variety of therapies has been tried for non-GORD-related functional oesophageal chest pain amongst patients with non-cardiac chest pain (NCCP). These include anticholinergics and muscle relaxants, botulinum toxin, psychotropic medications, cognitive-behavioural therapy, and surgery (133).

Trials of novel visceral sensitivity modifying agents for presumed visceral hyperalgesia as a cause of NCCP including theophylline, cilansetron a 5-HT_3 antagonist, tegaserod a partial 5-HT_4 agonist, octreotide, and fedotozine a peripherally acting κ-opioid agonist may demonstrate a cornerstone role, alone or in combination with a PPI (1).

Future Developments in Musculoskeletal Chest Pain

A careful history and examination by palpation or pressure should suggest a musculoskeletal cause for NCCP, although this does not *per se* rule out a more serious cardiac cause as they may coexist (134). Clinical predictors of musculoskeletal chest pain, including response to manual therapy, are currently under investigation for patients presenting with acute chest pain (135).

The role of radiological examination including MRI in musculoskeletal NCCP remains unproven, and newer imaging modalities are unlikely to ever be cost-effective, compared to focusing on understanding better the underlying mechanisms such as spinal referred pain (136).

Synopsis / Summary

Future developments in the assessment and management of patients with acute coronary syndrome (ACS) presenting to the Emergency Department (ED) with chest pain will include improved ECG analysis, novel biomarkers, newer imaging techniques, risk stratification tools, improved drugs, sonothrombolysis and stem cell transplantation.

Similarly, developments in patients presenting to the ED with chest pain suggesting a PE will include novel biomarkers, newer imaging techniques, risk stratification tools and safer

drugs. Additional strategies may include percutaneous mechanical thrombectomy and re-evaluation of the role of thrombolysis in submassive PE.

Developments in patients suspected of acute aortic dissection (AAD) presenting to ED with chest pain will again include novel biomarkers, plus newer imaging techniques such as contrast-enhanced ultrasound, endovascular treatment and combined interventional and surgical treatment.

Developments in gastrointestinal disease will include alternate endoscopic techniques, methods to differentiate non-gastro-oesophageal reflux disease (GORD) causes for pain, better recognition of functional heartburn, and validating new treatment modalities such as medication, cognitive-behavioural therapy and surgery. Finally, developments in musculoskeletal chest pain will focus on a greater understanding of underlying mechanisms, and the role, if any, for newer imaging techniques.

Most research on chest pain patients is thus focused on advances in the diagnosis and management of acute coronary syndrome, pulmonary embolism and acute aortic dissection, despite the fact that there is no significant difference at four years in mortality, ongoing chest pain, and quality of life between patients presenting to the emergency department with non-cardiac chest pain (NCCP) as opposed to cardiac. In addition, NCCP patients significantly outnumber patients presenting with an underlying cardiac cause, particularly to the primary care physician.

Table 1.

Future developments in patients with suspected acute coronary syndrome (ACS)

Improved ECG analysis
Novel biomarkers
Newer imaging techniques
Risk stratification tools
Improved drugs
Sonothrombolysis
Stem cell transplantation

Table 2.

Proposed new biomarkers for the diagnosis and risk stratification of patients with possible ACS

Copeptin

Myeloperoxidase (MPO)

Pregnancy associated plasma protein A (PaPP-A)

Placental growth factor (PlGF)

CD40 Ligand

Ischemia modified albumin (IMA)

Fatty acid binding protein

Free fatty acids (FFA)

Growth differentiation factor-15 (GDF-15)

Serum choline

Glycogen phosphorylase isoenzyme BB (GPBB)

High-sensitvity CRP (hsCRP)

Legend: ACS = acute coronary syndrome

Table 3.

Newer imaging modalities to identify ACS

Cardiac computed tomographic angiography (CCTA)

'Vulnerable plaque' analysis:

- CCTA
- Intravascular ultrasound (IVUS)
- Palpography and virtual histology
- Optical coherence tomography (OCT)
- Near infrared spectroscopy

Cardiac magnetic resonance imaging (CMR)

Positron emission tomography (PET)

Legend: ACS = acute coronary syndrome

Table 4.

Future developments in patients with suspected pulmonary embolism (PE)

Novel biomarkers
Newer imaging techniques
Risk stratification tools
Improved therapeutic agents
Percutaneous mechanical thrombectomy (PMT)
Re-evaluation of role of thrombolysis in submassive PE

Table 5.

Future developments in patients with suspected acute aortic dissection (AAD)

Novel biomarkers
Contrast-enhanced ultrasound (CEUS)
Endovascular treatment
Combined interventional and surgical treatment

Figure 1.

ECG body surface mapping (BSM) using up to 80 ECG leads

(reproduced with permission, Heartscape Technologies, Inc., Columbia, Maryland USA)

Figure 2

Computer screen shot of the attribute matching PE computer interface

(reproduced with permission, PREtest Consult Inc™)

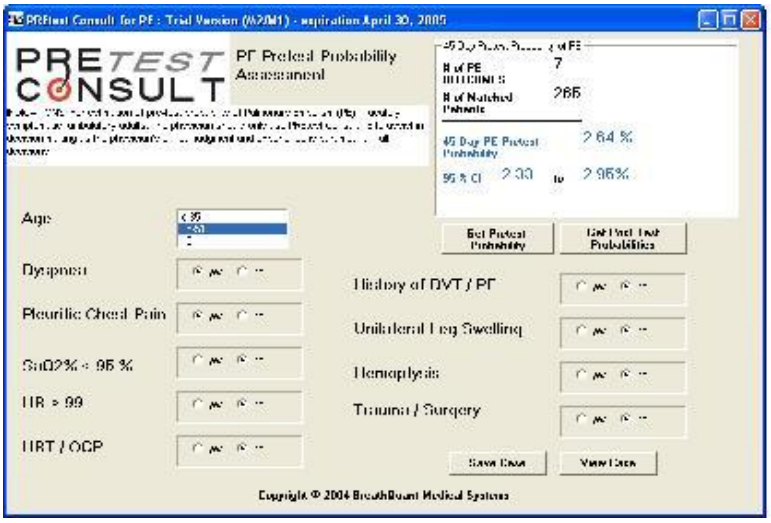
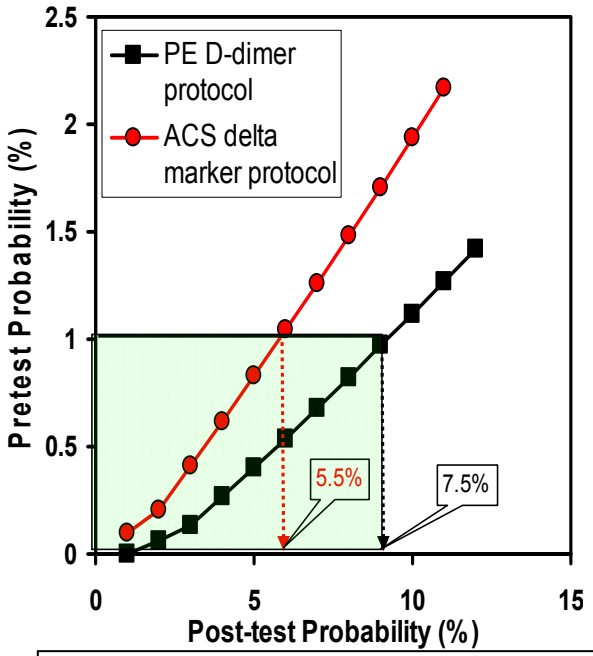


Figure 3.

Plot of pre-test probability on the Y-axis and the post-test probability on the X axis, for different tests (D-dimer and acute coronary syndrome ACS Δ), with different odds ratios. The green rectangle represents a post-test probability of <1%.

(reproduced with permission, PREtest Consult Inc™)



The two curves represent different tests, one D-dimer with a LR(-)=0.13 and the other serial biomarkers in ACS with LR(-)=0.20

The pre-test probabilities in the green rectangle would yield a post-test probability <1%.

The maximum safe pre-test probability is 7.5% for the D-dimer protocol. and 5.5% for the ACS biomarkers.

References

1. Eslick GD, Coulshed DS, Talley NJ. Diagnosis and treatment of noncardiac chest pain. *Nat Clin Pract Gastroenterol Hepatol*. 2005 Oct;2(10):463-72.
2. Eslick GD, Talley NJ. Natural history and predictors of outcome for non-cardiac chest pain: a prospective 4-year cohort study. *Neurogastroenterol Motil*. 2008 Sep;20(9):989-97.
3. Miller TD, Christian TF, Hopfenspirger MR, et al. Infarct size after acute myocardial infarction measured by quantitative tomographic 99mTc sestamibi imaging predicts subsequent mortality. *Circulation*. 1995 Aug 1;92(3):334-41.
4. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation*. 1990 Apr;81(4):1161-72.
5. Storrow AB, Gibler WB. Chest pain centers: diagnosis of acute coronary syndromes. *Ann Emerg Med*. 2000 May;35(5):449-61.
6. Pilote L, Granger C, Armstrong PW, et al. Differences in the treatment of myocardial infarction between the United States and Canada. A survey of physicians in the GUSTO trial. *Med Care*. 1995 Jun;33(6):598-610.
7. Graff LG, Dallara J, Ross MA, et al. Impact on the care of the emergency department chest pain patient from the chest pain evaluation registry (CHEPER) study. *Am J Cardiol*. 1997 Sep 1;80(5):563-8.
8. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med*. 2000 Apr 20;342(16):1163-70.
9. Terkelsen CJ, Lassen JF, Norgaard BL, et al. Reduction of treatment delay in patients with ST-elevation myocardial infarction: impact of pre-hospital diagnosis and direct referral to primary percutanous coronary intervention. *Eur Heart J*. 2005 Apr;26(8):770-7.
10. Ortolani P, Marzocchi A, Marrozzini C, et al. Clinical impact of direct referral to primary percutaneous coronary intervention following pre-hospital diagnosis of ST-elevation myocardial infarction. *Eur Heart J*. 2006 Jul;27(13):1550-7.
11. Zanini R, Aroldi M, Bonatti S, et al. Impact of prehospital diagnosis in the management of ST elevation myocardial infarction in the era of primary percutaneous coronary intervention: reduction of treatment delay and mortality. *J Cardiovasc Med*. 2008 Jun;9(6):570-5.
12. Hailer B, Naber CK, Koslowski B, et al. [STEMI network Essen--results after 1 year]. *Herz*. 2008 Mar;33(2):153-7.
13. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet*. 1994 Feb 5;343(8893):311-22.
14. Boersma E, Maas AC, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet*. 1996 Sep 21;348(9030):771-5.
15. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA*. 2000 Jun 14;283(22):2941-7.

16. Self WH, Mattu A, Martin M, et al. Body surface mapping in the ED evaluation of the patient with chest pain: use of the 80-lead electrocardiogram system. *Am J Emerg Med*. 2006 Jan;24(1):87-112.
17. Menown IB, Allen J, Anderson JM, et al. Early diagnosis of right ventricular or posterior infarction associated with inferior wall left ventricular acute myocardial infarction. *Am J Cardiol*. 2000 Apr 15;85(8):934-8.
18. Kornreich F, Montague TJ, Rautaharju PM. Body surface potential mapping of ST segment changes in acute myocardial infarction. Implications for ECG enrollment criteria for thrombolytic therapy. *Circulation*. 1993 Mar;87(3):773-82.
19. Owens C, McClelland A, Walsh S, et al. Comparison of value of leads from body surface maps to 12-lead electrocardiogram for diagnosis of acute myocardial infarction. *Am J Cardiol*. 2008 Aug 1;102(3):257-65.
20. Menown IB, Allen J, Anderson JM, et al. ST depression only on the initial 12-lead ECG: early diagnosis of acute myocardial infarction. *Eur Heart J*.2001 Feb;22(3):218-27.
21. Owens CG, McClelland AJ, Walsh SJ, et al. Prehospital 80-LAD mapping: does it add significantly to the diagnosis of acute coronary syndromes? *J Electrocardiology*. 2004;37 Suppl:223-32.
22. Carley SD, Jenkins M, Mackway Jones K. Body surface mapping versus the standard 12 lead ECG in the detection of myocardial infarction amongst emergency department patients: a Bayesian approach. *Resuscitation*. 2005 Mar;64(3):309-14.
23. Abboud S, Zlochiver S. High-frequency QRS electrocardiogram for diagnosing and monitoring ischemic heart disease. *J Electrocardiology*.2006 Jan;39(1):82-6.
24. Tragardh E, Schlegel TT. High-frequency QRS electrocardiogram. *Clin Physiol Funct Imaging*. 2007 Jul;27(4):197-204.
25. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation*. 2007 Nov 27;116(22):2634-53.
26. Apple FS, Wu AH, Mair J, et al. Future biomarkers for detection of ischemia and risk stratification in acute coronary syndrome. *Clin Chem*. 2005 May;51(5):810-24.
27. Wood FO, de Lemos JA, Wood FO, et al. Sorting through new biomarkers. *Curr Cardiol Rep*. 2008 Jul;10(4):319-26.
28. Steg PG, FitzGerald G, Fox KA, et al. Risk stratification in non-ST-segment elevation acute coronary syndromes: troponin alone is not enough. *Am J Med*. 2009 Feb;122(2):107-8.
29. Reichlin T, Hochholzer W, Stelzig C, et al. Incremental value of copeptin for rapid rule out of acute myocardial infarction. *J Am Coll Cardiol*. 2009 Jun 30;54(1):60-8.
30. Brennan ML, Penn MS, Van Lente F, et al. Prognostic value of myeloperoxidase in patients with chest pain. *N Engl J Med*. 2003 Oct 23;349(17):1595-604.
31. Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease: the present and the future. *J Am Coll Cardiol*. 2006 Jul 4;48(1):1-11.
32. Wu AH. Markers for early detection of cardiac diseases. *Scand J Clin Lab Invest Suppl*. 2005;240:112-21.
33. Ilva T, Lund J, Porela P, et al. Early markers of myocardial injury: cTnI is enough. *Clinica Chimica Acta*. 2009 Feb;400(1-2):82-5.
34. Rathore S, Knowles P, Mann AP, et al. Is it safe to discharge patients from accident and emergency using a rapid point of care Triple Cardiac Marker test to rule

out acute coronary syndrome in low to intermediate risk patients presenting with chest pain? *Eur J Intern Med*. 2008 Nov;19(7):537-40.
35. Ng SM, Krishnaswamy P, Morissey R, et al. Ninety-minute accelerated critical pathway for chest pain evaluation. *Am J Cardiol*. 2001 Sep 15;88(6):611-7.
36. Kontos MC, Anderson FP, Hanbury CM, et al. Use of the combination of myoglobin and CK-MB mass for the rapid diagnosis of acute myocardial infarction. *Am J Emerg Med*. 1997 Jan;15(1):14-9.
37. McCord J, Nowak RM, McCullough PA, et al. Ninety-minute exclusion of acute myocardial infarction by use of quantitative point-of-care testing of myoglobin and troponin I. *Circulation*. 2001 Sep 25;104(13):1483-8.
38. Dadkhah S, Sharain K, Sharain R, et al. The value of bedside cardiac multibiomarker assay in rapid and accurate diagnosis of acute coronary syndromes. *Critical Pathways in Cardiology: A Journal of Evidence-Based Medicine*. 2007 Jun;6(2):76-84.
39. Straface AL, Myers JH, Kirchick HJ, et al. A rapid point-of-care cardiac marker testing strategy facilitates the rapid diagnosis and management of chest pain patients in the emergency department. *Am J Clin Pathol*. 2008 May;129(5):788-95.
40. Newby LK, Storrow AB, Gibler WB, et al. Bedside multimarker testing for risk stratification in chest pain units: The chest pain evaluation by creatine kinase-MB, myoglobin, and troponin I (CHECKMATE) study. *Circulation*. 2001 Apr 10;103(14):1832-7.
41. Apple FS, Jesse RL, Newby LK, et al. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical issues for biochemical markers of acute coronary syndromes. *Circulation*. 2007 Apr 3;115(13):e352-5.
42. Apple FS, Pearce LA, Smith SW, et al. Role of monitoring changes in sensitive cardiac troponin I assay results for early diagnosis of myocardial infarction and prediction of risk of adverse events. *Clin Chem*. 2009 May;55(5):930-7.
43. Macrae AR, Kavsak PA, Lustig V, et al. Assessing the requirement for the 6-hour interval between specimens in the American Heart Association Classification of Myocardial Infarction in Epidemiology and Clinical Research Studies. *Clin Chem*. 2006 May;52(5):812-8.
44. Fesmire FM, Fesmire CE, Fesmire FM, et al. Improved identification of acute coronary syndromes with second generation cardiac troponin I assay: utility of 2-hour delta cTnI > or = +0.02 ng/mL. *J Emerg Med*. 2002 Feb;22(2):147-52.
45. Apple FS, Smith SW, Pearce LA, et al. Use of the bioMerieux VIDAS troponin I ultra assay for the diagnosis of myocardial infarction and detection of adverse events in patients presenting with symptoms suggestive of acute coronary syndrome. *Clin Chim Acta*. 2008 Apr;390(1-2):72-5.
46. Bassand JP, Hamm CW, Ardissino D et al. The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007 Jul;28(13):1598-660.
47. Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation*. 2006 Oct 17;114(16):1761-91.

48. Raman SV, Shah M, McCarthy B, et al. Multi-detector row cardiac computed tomography accurately quantifies right and left ventricular size and function compared with cardiac magnetic resonance. *Am Heart J*. 2006 Mar;151(3):736-44.
49. Rubinshtein R, Halon DA, Gaspar T, et al. Usefulness of 64-slice cardiac computed tomographic angiography for diagnosing acute coronary syndromes and predicting clinical outcome in emergency department patients with chest pain of uncertain origin. *Circulation*. 2007 Apr 3;115(13):1762-8.
50. Rubinshtein R, Halon DA, Gaspar T, et al. Usefulness of 64-slice multidetector computed tomography in diagnostic triage of patients with chest pain and negative or nondiagnostic exercise treadmill test result. *Am J Cardiol*. 2007 Apr 1;99(7):925-9.
51. Hollander JE, Chang AM, Shofer FS, et al. Coronary computed tomographic angiography for rapid discharge of low-risk patients with potential acute coronary syndromes. *Ann Emerg Med*. 2009 Mar;53(3):295-304.
52. Hollander JE, Litt HI, Chase M, et al. Computed tomography coronary angiography for rapid disposition of low-risk emergency department patients with chest pain syndromes. *Acad Emerg Med*. 2007 Feb;14(2):112-6.
53. Hoffmann U, Bamberg F, Chae CU, et al. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. *J Am Coll Cardiol*. 2009 May 5;53(18):1642-50.
54. Gallagher MJ, Raff GL. Use of multislice CT for the evaluation of emergency room patients with chest pain: the so-called "triple rule-out". *Catheter Cardiovasc Interv*. 2008 Jan 1;71(1):92-9.
55. Gallagher MJ, Ross MA, Raff GL, et al. The diagnostic accuracy of 64-slice computed tomography coronary angiography compared with stress nuclear imaging in emergency department low-risk chest pain patients. *Ann Emerg Med*. 2007 Feb;49(2):125-36.
56. Hollander JE, Chang AM, Shofer FS, et al. Coronary computed tomographic angiography for rapid discharge of low-risk patients with potential acute coronary syndromes. *Ann Emerg Med*. 2009 Mar;53(3):295-304.
57. Cury RC, Feutchner G, Pena CS, et al. Acute chest pain imaging in the emergency department with cardiac computed tomography angiography. *J Nucl Cardiol*. 2008 Jul-Aug;15(4):564-75.
58. Hoffmann U, Moselewski F, Nieman K, et al. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. *J Am Coll Cardiol*. 2006 Apr 18;47(8):1655-62.
59. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol*.2007 Jul 24;50(4):319-26.
60. Ambrose JA. In search of the "vulnerable plaque": can it be localized and will focal regional therapy ever be an option for cardiac prevention? *J Am Coll Cardiol*. 2008 Apr 22;51(16):1539-42.
61. Salah A, Moliterno DJ, Humphries R, et al. Role of cardiac computed tomography and magnetic resonance imaging in the evaluation of acute chest pain in the emergency department. *Int J Cardiovasc Imaging*. 2008 Mar;24(3):331-42.
62. Ingkanisorn WP, Kwong RY, Bohme NS, et al. Prognosis of negative adenosine stress magnetic resonance in patients presenting to an emergency department with chest pain. *J Am Coll Cardiol*. 2006 Apr 4;47(7):1427-32.

63. Di Cesare E, Battisti S, Riva A, et al. Parallel imaging and dobutamine stress magnetic resonance imaging in patients with atypical chest pain or equivocal ECG not suitable for stress echocardiography. *Radiol Med*. 2009 Mar;114(2):216-28.
64. Lockie T, Nagel E, Redwood S, et al. Use of cardiovascular magnetic resonance imaging in acute coronary syndromes. *Circulation*. 2009 Mar 31;119(12):1671-81.
65. Di Carli MF, Dorbala S. Cardiac PET-CT. *J Thorac Imaging*. 2007 Feb;22(1):101-6.
66. Di Carli MF, Dorbala S, Hachamovitch R. Integrated cardiac PET-CT for the diagnosis and management of CAD. *J Nucl Cardiol*. 2006 Mar-Apr;13(2):139-44.
67. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007 Jul;28(13):1598-660.
68. Kline JA, Zeitouni RA, Hernandez-Nino J, et al. Randomized trial of computerized quantitative pretest probability in low-risk chest pain patients: effect on safety and resource use. *Ann Emerg Med*. 2009 Jun;53(6):727-35 e1.
69. Goldman L, Weinberg M, Weisberg M, et al. A computer-derived protocol to aid in the diagnosis of emergency room patients with acute chest pain. *N Engl J Med*. 1982 Sep 2;307(10):588-96.
70. Selker HP, Beshansky JR, Griffith JL, et al. Use of the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) to assist with triage of patients with chest pain or other symptoms suggestive of acute cardiac ischemia. A multicenter, controlled clinical trial. *Ann Intern Med*. 1998 Dec 1;129(11):845-55.
71. Kennedy RL, Burton AM, Fraser HS, et al. Early diagnosis of acute myocardial infarction using clinical and electrocardiographic data at presentation: derivation and evaluation of logistic regression models. *Eur Heart J*. 1996 Aug;17(8):1181-91.
72. Mitchell AM, Garvey JL, Chandra A, et al. Prospective multicenter study of quantitative pretest probability assessment to exclude acute coronary syndrome for patients evaluated in emergency department chest pain units. *Ann Emerg Med*. 2006 May;47(5):447.
73. Kline JA, Johnson CL, Pollack CV, Jr., et al. Pretest probability assessment derived from attribute matching. *BMC Med Inform Decis Mak*. 2005;5:26.
74. Harrison RF, Kennedy RL. Artificial neural network models for prediction of acute coronary syndromes using clinical data from the time of presentation. *Ann Emerg Med*. 2005 Nov;46(5):431-9.
75. Kline J. Randomized trial of pretest probability in low risk patients with chest pain. *Ann Emerg Med*.2007;50:S78.
76. Goldman L, Cook EF, Johnson PA, et al. Prediction of the need for intensive care in patients who come to the emergency departments with acute chest pain. *N Engl J Med*. 1996 Jun 6;334(23):1498-504.
77. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA*. 2000 Aug 16;284(7):835-42.
78. Hess EP, Thiruganasambandamoorthy V, Wells GA, et al. Diagnostic accuracy of clinical prediction rules to exclude acute coronary syndrome in the emergency department setting: a systematic review. *CJEM*. 2008 Jul;10(4):373-82.
79. Cullen L, Than M, Brown AFT, et al. A comprehensive standardised data definitions set for acute coronary syndrome research in emergency departments in Australasia. *Emerg. Med. Australas*. 2010;22:000-000.

80. Gurbel PA, Bliden KP, Hiatt BL, et al. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation*. 2003 Jun 17;107(23):2908-13.
81. Lau WC, Gurbel PA, Watkins PB, et al. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. *Circulation*. 2004 Jan 20;109(2):166-71.
82. Morrow DA, Wiviott SD, White HD, et al. Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction. *Circulation*. 2009 Jun 2;119(21):2758-64.
83. Price MJ. Bedside evaluation of thienopyridine antiplatelet therapy. *Circulation*. 2009 May 19;119(19):2625-32.
84. Thomas D, Giugliano RP. Antiplatelet therapy in percutaneous coronary intervention: integration of prasugrel into clinical practice. *Crit Pathways Cardiol*. 2009 Mar;8(1):12-9.
85. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009 Sep 10;361(11):1045-57.
86. Gibson CM, Kirtane AJ, Murphy SA, et al. Early initiation of eptifibatide in the emergency department before primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: results of the Time to Integrilin Therapy in Acute Myocardial Infarction (TITAN)-TIMI 34 trial. *Am Heart J*. 2006 Oct;152(4):668-75.
87. Zeymer U, Zahn R, Schiele R, et al. Early eptifibatide improves TIMI 3 patency before primary percutaneous coronary intervention for acute ST elevation myocardial infarction: results of the randomized integrilin in acute myocardial infarction (INTAMI) pilot trial. *Eur Heart J*. 2005 Oct;26(19):1971-7.
88. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med*. 2001 Jun 21;344(25):1895-903.
89. Pels K, Schroder J, Witzenbichler B, et al. Prehospital versus periprocedural abciximab in ST-elevation myocardial infarction treated by percutaneous coronary intervention. *Eur J Emerg Med*. 2008 Dec;15(6):324-9.
90. Giugliano RP, Newby LK, Harrington RA, et al. The early glycoprotein IIb/IIIa inhibition in non-ST-segment elevation acute coronary syndrome (EARLY ACS) trial: a randomized placebo-controlled trial evaluating the clinical benefits of early front-loaded eptifibatide in the treatment of patients with non-ST-segment elevation acute coronary syndrome--study design and rationale. *Am Heart J*. 2005 Jun;149(6):994-1002.
91. Kaul S. Sonothrombolysis: a universally applicable and better way to treat acute myocardial infarction and stroke? Who is going to fund the research? *Circulation*. 2009 Mar 17;119(10):1358-60.
92. Siegel RJ, Suchkova VN, Miyamoto T, et al. Ultrasound energy improves myocardial perfusion in the presence of coronary occlusion. *J Am Coll Cardiol*.2004 Oct 6;44(7):1454-8.
93. Atoui R, Shum-Tim D, Chiu RC, et al. Myocardial regenerative therapy: immunologic basis for the potential "universal donor cells". *Ann Thorac Surg*. 2008 Jul;86(1):327-34.

94. Hirsch A, Nijveldt R, van der Vleuten PA, et al. Intracoronary infusion of autologous mononuclear bone marrow cells in patients with acute myocardial infarction treated with primary PCI: Pilot study of the multicenter HEBE trial. *Catheter Cardiovasc Interv*. 2008 Feb 15;71(3):273-81.
95. Atoui R, Shum-Tim D, Chiu RC. Myocardial regenerative therapy: immunologic basis for the potential "universal donor cells". *Ann Thorac Surg*. 2008 Jul;86(1):327-34.
96. Than MP, Helm J, Calder K, et al. Comparison of high specificity with standard versions of a quantitative latex D-dimer test in the assessment of community pulmonary embolism: HaemosIL D-dimer HS and pulmonary embolism. *Thromb Res*. 2009 Jun;124(2):230-5.
97. Nordenholz KE, Mitchell AM, Kline JA. Direct Comparison of the Diagnostic Accuracy of Fifty Protein Biological Markers of Pulmonary Embolism for Use in the Emergency Department. *Acad Emerg Med*. 2008 Aug 10.
98. Linkins LA, Bates SM, Ginsberg JS, et al. Use of different D-dimer levels to exclude venous thromboembolism depending on clinical pretest probability. *J Thromb Haemost*. 2004 Aug;2(8):1256-60.
99. Suleyman T, Tevfik, P., Abdulkadir, G., Ahmet, M., Celal, T., Murat, T., Suleyman, C.K., Esin, Y., Suha, T., and Utku, U.. . Ischemia-modified albumin in the diagnosis of pulmonary embolism: an experimental study. *Am J Emerg Med*. 2009;27(6):635-40
100. Sainaghi PP, Alciato F, Carnieletto S, et al. Gas6 evaluation in patients with acute dyspnea due to suspected pulmonary embolism. *Respir Med*. 2009 Apr;103(4):589-94.
101. Mitchell AM, Nordenholz KE, Kline JA. Tandem measurement of D-dimer and myeloperoxidase or C-reactive protein to effectively screen for pulmonary embolism in the emergency department. *Acad Emerg Med*. 2008 Sep;15(9):800-5.
102. Collart JP, Roelants V, Vanpee D, et al. Is a lung perfusion scan obtained by using single photon emission computed tomography able to improve the radionuclide diagnosis of pulmonary embolism? *Nucl Med Commun*. 2002 Nov;23(11):1107-13.
103. Lemb M, Pohlabeln H. Pulmonary thromboembolism: a retrospective study on the examination of 991 patients by ventilation/perfusion SPECT using Technegas. *Nuklearmedizin*. 2001 Dec;40(6):179-86.
104. Stein PD, Gottschalk A, Sostman HD, et al. Methods of Prospective Investigation of Pulmonary Embolism Diagnosis III (PIOPED III). *Semin Nucl Med*. 2008 Nov;38(6):462-70.
105. Morris TA, Macfarlane, D.J., Eisenberg, P.R. et al. . Clinical diagnostic imaging of pulmonary emboli using radiolabeled anticrosslinked fibrin antibodies ThromboView^{R}. *Chest*. [Abstract]. 2006;130:S275.
106. Macfarlane D, Socrates A, Eisenberg P, et al. Imaging of deep venous thrombosis in patients using a radiolabelled anti-D-dimer Fab' fragment (99mTc-DI-DD3B6/22-80B3): results of a phase I trial. *Eur J Nucl Med Mol Imaging*. 2009 Feb;36(2):250-9.
107. Kline JA, Novobilski AJ, Kabrhel C, et al. Derivation and validation of a Bayesian network to predict pretest probability of venous thromboembolism. *Ann Emerg Med*. 2005 Mar;45(3):282-90.
108. Runyon MS, Webb WB, Jones AE, et al. Comparison of the unstructured clinician estimate of pretest probability for pulmonary embolism to the Canadian score and the Charlotte rule: a prospective observational study. *Acad Emerg Med*. 2005 Jul;12(7):587-93.

109. Baxt WG, Shofer FS, Sites FD, et al. A neural computational aid to the diagnosis of acute myocardial infarction. *Ann Emerg Med*.2002 Apr;39(4):366-73.
110. Kline JA, Mitchell AM, Kabrhel C, et al. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. *J Thromb Haemost*. 2004 Aug;2(8):1247-55.
111. Kline J, Courtney D, Than M. Accuracy of Very Low Pretest Probability Estimates for Pulmonary Embolism Using the Method of Attribute Matching Compared with the Wells' Score. *Acad Emerg Med*. 2009:in publication.
112. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. *N Engl J Med*. 1980 May 15;302(20):1109-17.
113. Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost*. 2008 May;6(5):772-80.
114. Kline JA, Johns KL, Colucciello SA, et al. New diagnostic tests for pulmonary embolism. *Ann Emerg Med*. 2000 Feb;35(2):168-80.
115. Brown MD, Lau J, Nelson RD, et al. Turbidimetric D-dimer test in the diagnosis of pulmonary embolism: a metaanalysis. *Clin Chem*. 2003 Nov;49(11):1846-53.
116. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med*. 2004 Apr 20;140(8):589-602.
117. Eid-Lidt G, Gaspar, J., Sandoval, J., Damas de los Santos, F., Pulido, T., González Pacheco, H., Martínez-Sánchez, C.. Combined Clot Fragmentation and Aspiration in Patients With Acute Pulmonary Embolism. *Chest.* 2008;134(1):54-60.
118. Wan S, Quinlan DJ, Agnelli G, et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation*. 2004 Aug 10;110(6):744-9.
119. Stevinson BG, Hernandez-Nino J, Rose G, et al. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. *Eur Heart J*. 2007 Oct;28(20):2517-24.
120. Tran TP, Khoynezhad A. Current management of type B aortic dissection. *Vasc Health Risk Manag*. 2009;5(1):53-63.
121. Suzuki T, Distante A, Zizza A, et al. Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) experience. *Circulation*. 2009 May 26;119(20):2702-7.
122. Patel DP, Arora, R.R.. Pathophysiology, diagnosis, and management of aortic dissection. *Ther Adv Cardiovasc Dis*. 2008;2:439.
123. Suzuki T, Katoh H, Tsuchio Y, et al. Diagnostic implications of elevated levels of smooth-muscle myosin heavy-chain protein in acute aortic dissection. The smooth muscle myosin heavy chain study. *Ann Intern Med*. 2000 Oct 3;133(7):537-41.
124. Suzuki T, Distante A, Zizza A, et al. Preliminary experience with the smooth muscle troponin-like protein, calponin, as a novel biomarker for diagnosing acute aortic dissection. *Eur Heart J*. 2008 Jun;29(11):1439-45.
125. Sodeck G, Domanovits H, Schillinger M, et al. D-dimer in ruling out acute aortic dissection: a systematic review and prospective cohort study. *Eur Heart J*. 2007 Dec;28(24):3067-75.
126. Salvagno GL, Targher G, Franchini M, et al. Plasma D-dimer in the diagnosis of acute aortic dissection. *Eur Heart J*. 2008 May;29(9):1207.

127. Clevert D-A, Weckbach, S., Kopp, R., et al. Imaging of aortic lesions with color coded duplex sonography and contrast-enhanced ultrasound versus multislice computed tomography (MS-CT) angiography. *Clin Hemorheol Microcirc*. 2008;40(4):267-79.
128. Svensson LG, Kouchoukos NT, Miller DC, et al. Expert consensus document on the treatment of descending thoracic aortic disease using endovascular stent-grafts. *Ann Thorac Surg*. 2008 Jan;85(1 Suppl):S1-41.
129. Liu JC, Zhang JZ, Yang J, et al. Combined interventional and surgical treatment for acute aortic type a dissection. *Int J Surg*. 2008 Apr;6(2):151-6.
130. Halpern EJ. Triple-rule-out CT angiography for evaluation of acute chest pain and possible acute coronary syndrome. *Radiology*. 2009 Aug;252(2):332-45.
131. Takakuwa KM, Halpern EJ, Gingold EL, et al. Radiation dose in a "triple rule-out" coronary CT angiography protocol of emergency department patients using 64-MDCT: the impact of ECG-based tube current modulation on age, sex, and body mass index. *AJR Am J Roentgenol*. 2009 Apr;192(4):866-72.
132. Modlin IM, Hunt RH, Malfertheiner P, et al. Diagnosis and Management of Non-Erosive Reflux Disease - The Vevey NERD Consensus Group. *Digestion*. 2009 Jun 17;80(2):74-88.
133. Schmulson MJ, Valdovinos MA. Current and future treatment of chest pain of presumed esophageal origin. *Gastroenterol Clin North Am*. 2004 Mar;33(1):93-105.
134. Christensen HW, Vach W, Gichangi A, et al. Cervicothoracic angina identified by case history and palpation findings in patients with stable angina pectoris. *J Manipulative Physiol Ther*. 2005 Jun;28(5):303-11.
135. Stochkendahl MJ, Christensen HW, Vach W, et al. Diagnosis and treatment of musculoskeletal chest pain: design of a multi-purpose trial. *BMC Musculoskelet Disord*. 2008;9:40. Available from www.biomedcentral.com/1471-2474/9/40 (Accessed October 2009)
136. Harding G, Yelland M. Back, chest and abdominal pain - is it spinal referred pain? *Aust Fam Physician*. 2007 Jun;36(6):422-3, 5, 7-9.